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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,288	12/14/2006	James C. Jamieson	R131 1010.1	2936

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WOMBLE CARLYLE SANDRIDGE & RICE, PLLC
ATTN: PATENT DOCKETING
P.O. BOX 7037
ATLANTA, GA 30357-0037

EXAMINER	
KIM, TAEYOON	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,288	JAMIESON ET AL.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35 and 39-54* is/are pending in the application.

4a) Of the above claim(s) *39-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/14/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on 2/11/2010 has been received and entered into the case.

Claims 1-30, 32-34, 36-38 are canceled, claims 39-54 have been withdrawn from consideration as being drawn to non-elected subject matter, and claims 31 and 35 have been considered on the merits. All arguments have been fully considered.

Claim Objections

The claim objection has been withdrawn due to the amendment.

Claim Rejections - 35 USC § 112

The claim rejection under 35 U.S.C.§112 has been withdrawn due to the amendment.

Claim Rejections - 35 USC § 102

The claim rejection under 35 U.S.C.§102 has been withdrawn due to the amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " *(Wands,* 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *(Wands,* 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The instant claims are directed to a method of administering a patient in need of reducing serum levels of triglycerides or VLDL with a therapeutically effective amount of an autophagocytosis inducing compound selected from MAP-LC3, GATE-16 or Class III PI3 kinase.

The claimed invention can not be considered to be enabled given the limited showing in the specification. First there is no clear reduction to practice of the claimed invention as no disclosed embodiment appear to have actually effectively reduced serum level of triglycerides or VLDL in a patient by administering MAP-LC3, GATE16 or Class III PI3 kinase.

The specification only presents prophetic embodiment, assuming that the method of current invention would be enabled without undue experimentation. However, applicant's

assertion that MAP-LC3, GATE16 or Class III PI3 kinase would reduce the serum level of triglycerides or VLDL is not enabled by the specification as filed.

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable -Tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997).

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Applicant appears to claim that any one molecule selected from MAP1LC3, GATE16 or Class III PI3 kinase, which is known to be involved in the formation of autophagosomes, would

necessarily induce autophagocytosis intracellularly resulting in reducing serum level of triglycerides or VLDL (claim 31) or treating/preventing hypercholesterolemia (claim 35).

While the specification discloses some evidence to link EPA's effect in reducing triglycerides and VLDL from serum mediated by the increased Golgi associated vacuoles (GAVs) formation, and subsequent degradation, the specification failed to provide an enabling embodiment to show each of these claimed molecules can induce the formation of autophagy intracellularly, or prevent/treat hypercholesterolemia if administered alone in sufficient amount (therapeutically effective amount).

The specification discloses that the pulse-chase study with EPA-treated cells (apoB100 transfected McA-RH7777 cells), which appears to reduce the VLDL assembly compared to oleate-treated cells, resulted in increased [^{35}S]-apoB100 species in microsomal lumen (p.34-35; Example 1). The specification subsequently discloses Examples 2-8 to show that EPA treatment promotes post-ER degradation of ApoB100, and the analyses on lipid/lipoprotein particles in the Golgi and associated vacuoles (GAV), showing immunocytochemical localization of apoB and Map1LC3 on GAVs, thus concluding that EPA treatment enhances autophagy formation.

Based on this observation, Applicant appears to assume that the autophagosome formation would necessarily and sufficiently reduce the formation of VLDL assembly, and thus, further assume that molecules involved in the formation such as MAP1LC3, GATE-16 or Class III PI3 kinase, would necessarily and sufficiently induce the formation of autophagy, even with one such protein administered, and by-pass the mechanism underlying the effect of EPA treatment, resulting in the intended purposes of the current invention.

However, the current specification failed to provide any guidance or working example other than EPA that the claimed molecules, either as nucleic acids or as proteins, would induce the formation of autophagosomes upon the administration to a patient in need of reducing serum triglycerides and/or VLDL, or suffering hypercholesterolemia.

The state of the prior art is relatively high in terms of autophagy formation, and various molecules involved in the formation have been identified in yeast and mammalian cells. However, it is still far from complete understanding of the underlying mechanism of autophagy.

According to the review article by Yoshimori et al. (2004, BBRC), there are several identified molecules involved in autophagy formation including the listed molecules (i.e. MAP1LC3, GABARAP, GATE-16 and Class III PI3 kinase) in the instant claims (see entire document; p.455-456). It appears that the formation of autophagy does not rely on a single molecule to initiate the formation, rather it is a multiplayer event.

Considering the nature of the mechanism requiring multiplayers in the formation of autophagosomes, it is highly unpredictable that any single molecule, even if it is known to participate in the formation of autophagosomes, would induce such formation without other players if it is in excess amount. Thus, the amount of the endogenous molecules would be the limiting factor, and unless the addition of a single molecule (i.e. MAP1LC3, GATE-16 or Class III PI3 kinase) results in up-regulation of other endogenous proteins/molecules participating in the formation of autophagosomes.

Furthermore, these molecules are known to be essential for the formation of autophagosomes, but it is highly unpredictable whether one molecule is sufficient to induce autophagy in the cells without undue experimentation.

Mizushima et al. (2004, Molecular Biology of the Cell) teach the overexpressing of LC3 (MAP1LC3) in F9 cells does not further induce autophagosomes compared to normal F9 cells in the absence of starvation (see Fig. 1). When the cells are starved to induce autophagy, LC3 overexpressed cells do not show any difference compared control cells (see Fig. 1). This result indicates that excess of LC3 overexpressed in the cells did not enhance autophagy or increased autophagosomes formation.

Kirisako et al. (1999, Journal of Cell Biology) teach that Apg8p is necessary for the autophagy, however, it is clear that the increase of Apg8p is not sufficient for the induction of autophagy, because overexpression of Apg8p did not induce autophagy under growing condition (p. 445, left col.). Although the data were obtained from yeast, however, since MAP1LC3 along with GATE-16 and GABARAP is known mammalian homologs of Apg8p according to Tanida et al. (2003, BBRC)(see abstract), Mizushima et al. (supra; abstract) and Yoshimori et al. (supra; p.455), and therefore, based on the teaching of Kirisako et al., it is highly unpredictable that any of these mammalian homologs of Apg8p is able to induce autophagy by overexpression.

The above teaching from Mizushima et al. and Kirisako et al. clearly show that the molecules, particularly LC3 or Apg8, in the claimed invention do not sufficiently induce formation of autophagosomes.

The amount of "undue experimentation" is enormous considering the complexity of the mechanisms, number of players/molecules involved in the mechanisms, and premature understanding of the mechanism in the art.

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of its unpredictability, the prior art teaching contradicting results to the claimed invention, and lack of guidance or working examples in the specification, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed, to its fully-claimed scope, without undue experimentation.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 5:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Primary Examiner, Art Unit 1651